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Preparation of New Benzothiazoles. Acid Anhydride and Acid Chloride Derivatives of Di-o-amino-phenyl disulfide

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY

By

ARTHUR STULL, B.S., A.M.

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TABLE OF CONTENTS

Abstract of dissertation 5
Flow sheets .....
Discussion 6
Experimental 12
Di-*o*-nitrophenyl-disulfide 12
Zinc salt of *o*-aminothiophenol 12
Hydrochloride of *o*-aminothiophenol 12
Di-*o*-aminophenyl-disulfide 12
2-Phenyl-benzothiazole 13, 15, 16
2-(*m*-*p*-Methylene-dioxy-phenyl)-benzothiazole 14
2-(*p*-Hydroxy *m*-methoxy-phenyl)-benzothiazole 14, 16
2-α-Furyl-benzothiazole 14, 20, 22
Benzothiazole 15
Benzophenone chloride and *o*-aminothiophenol 17
Ketones and *o*-aminothiophenol 17
2-2′(*p*-Phenylene)-bis-benzothiazole 18
Bis-benzothiazole 18
Pyromucyl chloride 19
α-Thiophenic acid 19
α-Thienyl chloride 20
2-α-Thienyl-benzothiazole 20, 21
Bis-(pyromucyl-anilide)-*o*-disulfide 21
Bis-(α-thiophen-anilide)-*o*-disulfide 21
Diphthalimidophenyl-*o*-disulfide 22
Bis-(glutaranilic acid)-*o*-disulfide 23
Bis-(succinanilic acid)-*o*-disulfide 24
Bis-(maleanilic acid)-*o*-disulfide 24
Bis-(camphoranilic acid)-*o*-disulfide 25
Bis-(ethyl-oxanilate)-*o*-disulfide 25
Bis-(oxanilamide)-*o*-disulfide 26
Bis-(oxanilide)-*o*-disulfide) 26
Benzothiazole-2-carboxylic acid 27
Bibliography 27
Vita 29

Preparation of New Benzothiazoles. Acid Anhydride and Acid Chloride Derivatives of Di-o-aminophenyl-disulfide.

Abstract

August William von Hofmann,[2] to whom belongs the credit of the discovery of the benzothiazoles, investigated a number of the compounds of this series. Among other methods, he stated that benzothiazoles resulted from the action of aldehydes on *o*-aminothio-phenols.[10] We were interested in these sulfur compounds on account of observations made by Fränkel, [36, 37, 38] Scheibler,[35] and many others that sulfur in the divalent, unoxidized state, or in unsaturated cyclic union imparted to compounds therapeutic properties.

Di-*o*-aminophenyl-disulfide, first prepared by Hofmann[2] in 1879, has been recommended by McDonagh[34] under the name of Intramine for the treatment of spirochaetal diseases. We have prepared a number of acid anhydride and acid chloride derivatives of this compound, several of which on reduction gave benzothiazole derivatives.

We were also interested in seeing whether it was possible to prepare the reduced benzothiazoles, namely, benzothiazolines. Claasz[31] claimed the formation of these benzothiazolines by the action of aldehydes on *o*-aminophenyl-mercaptan hydrochloride and as this was contradictory to Hofmann's former observation,[10] namely, that benzothiazoles resulted in the reaction between *o*-aminophenyl-mercaptan and aldehydes, we have investigated this reaction and have found that only benzothiazoles result. 2-Phenyl-benzothiazole resulted both from the action of benzaldehyde on *o*-aminothiophenol and from the action of benzal chloride on *o*-aminothiophenol.

2-Phenyl-benzothiazole (rosenkörper) has a pleasant odor similar to geraniums or tea roses while most of its derivatives are practically odorless. Since the furane and thiophene derivatives possess many similar physical and chemical proper-

ties to benzene, it seemed of interest to see if there was any relation in regard to the physiological property of odor. Therefore the analogues of 2-phenyl-benzothiazole with the 2-phenyl group substituted respectively by the thiophene and furane nucleus were prepared. These derivatives have an odor very similar to 2-phenyl-benzothiazole (rosenkörper) showing that the similarity extends to physiological action and it adds some light on the relation between structure and odor in 2-phenyl-benzothiazole.

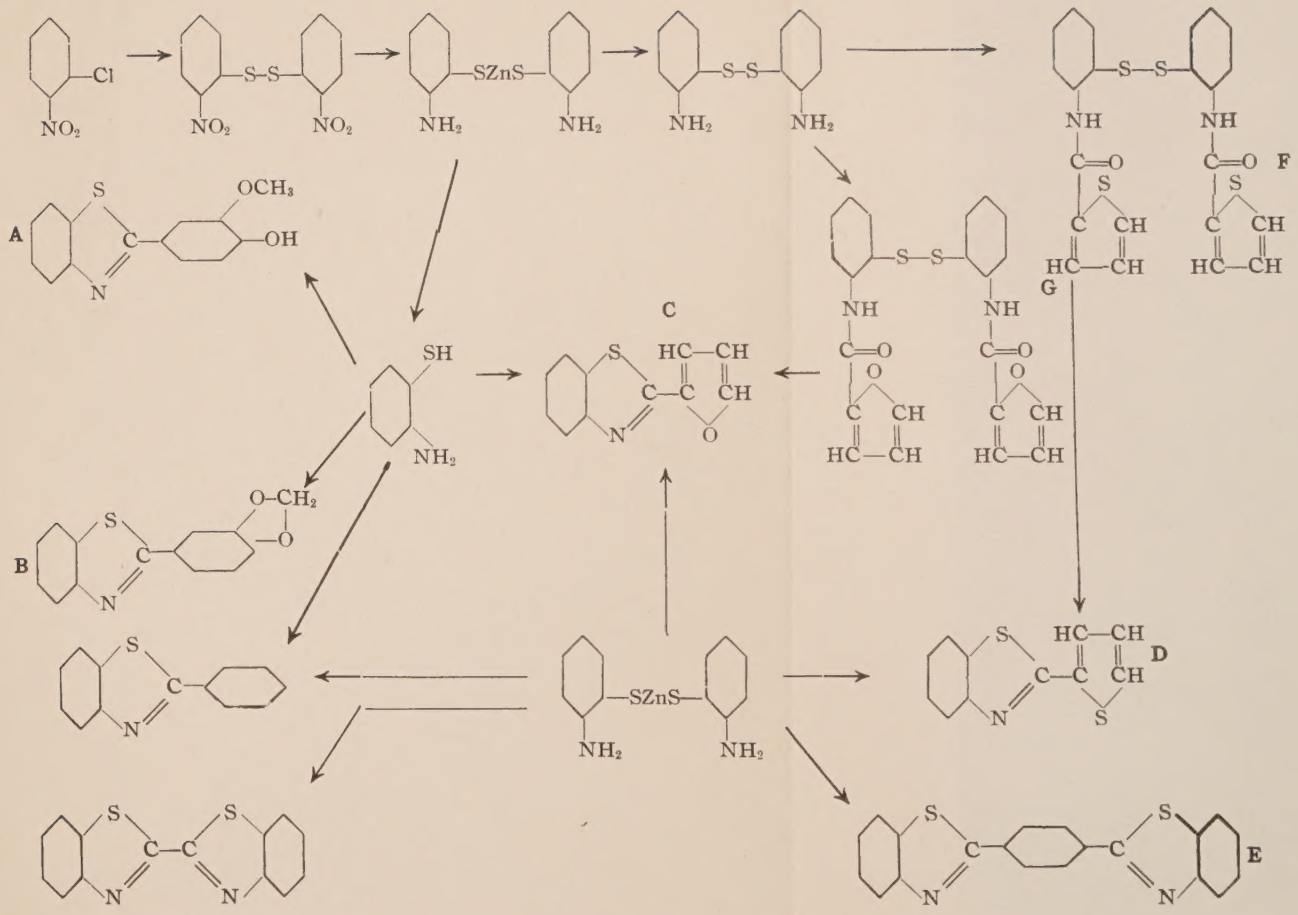
The following new compounds were prepared during the course of the investigation.

A 2-(*p*-Hydroxy *m*-methoxy phenyl)-benzothiazole
B 2-(*m-p*-Methylenedioxy phenyl)-benzothiazole
C 2-(α-Furyl)-benzothiazole
D 2-(α-Thienyl)-benzothiazole
E 2-2′-(*p*-Phenylene)-bis-benzothiazole
F Bis-(α-thiophenanilide)-*o*-disulfide
G Bis-(pyromucylanilide)-*o*-disulfide
H Diphthalimido phenyl-*o*-disulfide
K Bis-(succinanilic acid)-*o*-disulfide
L Bis-(glutaranilic acid)-*o*-disulfide
M Bis-(maleanilic acid)-*o*-disulfide
N Bis-(camphoranilic acid)-*o*-disulfide
P Bis-(ethyl oxanilate)-*o*-disulfide
R Bis-(oxanilamide)-*o*-disulfide
S Bis-(oxanilide)-*o*-disulfide

Discussion

Preparation of o-amino-thiophenol.

Hofmann[7] described the preparation of *o*-aminothiophenol by the fusion of bis-benzothiazole or 2-phenyl-benzothiazole with potassium hydroxide. The later method was recommended by Vanino.[46] Wohlfahrt[21] described the production of di-nitrophenyl-disulfide from *o*-nitrochlor-benzene and *p*-nitrochlor-benzene. Schultz and Beyschlag[28] prepared disulfides of toluene diamines. Bogert and Snell[42] described the


Cl
NO2
S–S
SZnS
NH2
SH
OCH3
OH
O–CH2
NH
C=O
CH
HC—CH
A
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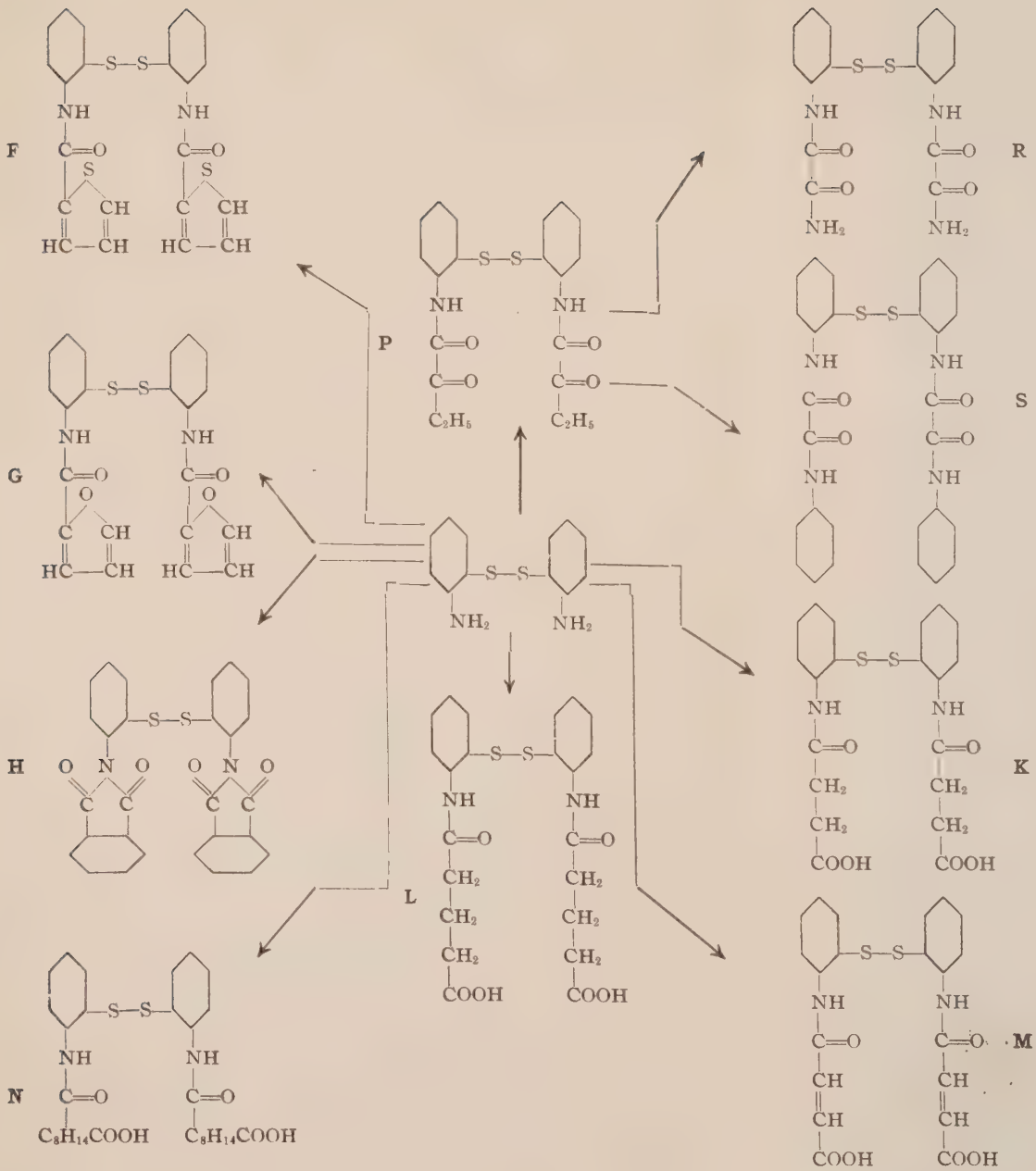
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formation of the zinc salt of *o*-aminothiophenol by treatment of a glacial acetic acid solution of di-*o*-nitrophenyl-disulfide with zinc dust. They have also prepared di-*o*-aminophenyl-disulfide[43] by passing air through the ammonium hydroxide solution of the zinc salt of *o*-aminothiophenol, and by fusing the zinc salt with benzoyl chloride have prepared 2-phenyl-benzothiazole.[44] Claasz[21] recommended the production of *o*-aminothiophenol-hydrochloride by reduction of the di-*o*-nitrophenyl-disulfide dissolved in a mixture of acetic and hydrochloric acids with granulated tin. The tin was precipitated from the diluted solution by hydrogen sulfide and the hydrochloride of *o*-aminothiophenol separated on concentration to a small volume. A convenient method for the formation of the *o*-aminothiophenol was to treat a hot glacial acetic acid solution of the zinc salt with hydrogen sulfide. The zinc was filtered off as the sulfide leaving a glacial acetic acid solution of the *o*-aminothiophenol.

Preparation of benzothiazoles from aldehydes and o-aminothiophenol.

Benzaldehyde was added to a warm glacial acetic acid solution of the *o*-aminothiophenol. It seemed to make no difference whether the aldehyde was added before or after the precipitation of the zinc. On dilution of the acetic acid solution, a precipitate resulted which on recrystallization had the characteristic odor of 2-phenyl-benzothiazole and was identical with it. It was thought that the reduced compound might first have formed and during the purification to have been oxidized to the 2-phenyl-benzothiazole. Therefore an unsuccessful attempt was made to acetylate the compound by the addition of acetic anhydride to the glacial acetic acid solution in the presence of the hydrogen sulfide. No evidence of any action occurred and 2-phenyl-benzothiazole was again the product. Immediately after the precipitation from the acetic acid solution, the precipitate was also treated with acetic anhydride, but still no action occurred and only 2-phenyl-benzothiazole resulted. In a similar manner *o*-aminothiophenol was condensed with piperonal giving 2-(*m-p*-methylene-dioxy-

phenyl)-benzothiazole and with vanillin there resulted 2-(*p*-hydroxy-*m*-methoxy-phenyl)-benzothiazole. In the case of fural, the aldehyde was added to the cool glacial acetic acid solution as this method gave a product more free from impurities, namely, 2-α-furyl-benzothiazole.

Claasz[30] first claimed the formation of benzothiazoline in the reaction between formaldehyde and *o*-aminothiophenol hydrochloride. He reported a yellow oil b. p., 270°. We repeated his exact procedure and failed to find any trace of benzothiazoline. The product was a yellow oil with the typical odor of nitrogen bases and boiled at 230°, which is the boiling point of benzothiazole. Later in the case of benzaldehyde,[32] he claimed the formation of 2-phenyl-benzothiazoline, softening at 105°, melting 108–109°. Repeating his procedure by adding a dilute alcohol solution to a water solution of the hydrochloride of *o*-aminothiophenol, the product had the typical geranium odor of 2-phenyl-benzothiazole, melted at 114° cor. and gave the same mixed melting point as 2-phenyl-benzothiazole prepared from benzalaniline and sulfur.[40] It was identical in every respect with 2-phenyl-benzothiazole. We repeated the procedure of Claasz in the case of vanillin and obtained a practically colorless product identical with the 2-(*p*-hydroxy-*m*-methoxy-phenyl)-benzothiazole formerly obtained, melting at 175.5° cor. Claasz reported yellow flakes m. p., 163–165°. In most cases the compounds prepared by Claasz by this method did not give sharp melting points and evidently had not been recrystallized to a constant melting point.

2-Phenyl-benzothiazole from benzal chloride.

If it were possible to form 2-phenyl-benzothiazoline, it seemed that the reaction between benzal chloride and *o*-aminothiophenol should give it. However, when the glacial acetic acid solution of the *o*-aminothiophenol was treated with benzal chloride, 2-phenyl-benzothiazole again resulted. Likewise from a dry fusion of the zinc salt of *o*-aminothiophenol and benzal chloride, 2-phenyl-benzothiazole resulted.

In a further attempt to see if the reduced benzothiazoline

could be formed, the zinc salt of *o*-aminothiophenol was fused with benzophenone chloride. No reaction took place. A similar unsuccessful attempt was made to carry out the reaction in a glacial acetic acid solution.

Since aldehydes on condensation with *o*-aminothiophenol gave benzothiazoles, we tried to see if a reaction would take place between *o*-aminothiophenol and ketones to form benzothiozolines. Michler's ketone, on account of its tendency for condensations was added to a glacial acetic acid solution of the thiophenol, but the ketone was recovered unchanged. Likewise no reaction occurred with acetone, the *o*-aminothiophenol being recovered.

2-α-Furyl-benzothiazole was also prepared by the fusion of the zinc salt of *o*-aminothiophenol and pyromucyl chloride. It gave a product identical with that prepared from fural and *o*-aminothiophenol and added further proof of the formation of benzothiazoles in the reaction between aldehydes and *o*-aminothiophenols. 2-α-Thienyl-benzothiazole was prepared by the action of α-thienyl chloride on the zinc salt of *o*-aminothiophenol. Both these products had an odor similar to geraniums or tea roses and similar to 2-phenyl-benzothiazole. The 2-α-thienyl-benzothiazole had the strongest odor. The melting points of the three products were within a 15° range. The odor of these benzothiazoles seemed to be dependent on the presence of a ring system at position 2. Probably the 5 or 6 member rings modified the strong odor of the parent substance, benzothiazole, sufficiently to give the pleasant "rosenkörper" odor.

Derivatives of 2-phenyl-benzothiazole have a very weak odor. Bogert and Meyer[41] reported *p*-tolyl-benzothiazole as having a slight odor when moistened with alcohol, suggestive of "rosenkörper." In 2-(*p*-hydroxy-*m*-methoxy-phenyl)-benzothiazole there was a weak vanillin type of odor, while the 2-(*m*-*p*-methylene-dioxy-phenyl)-benzothiazole had a faint sweet odor.

Hofman[9] prepared a compound from phthalyl-chloride and and *o*-amino-thiophenol m. p., 112°. It was evidently pre-

pared from the *o*-phthalyl-chloride. It was of interest to us to prepare the compound from terephthalyl-chloride[45] to see if there was any change in odor from 2-phenyl-benzothiazole by doubling the benzothiazole part of the molecule. A colorless, crystalline compound, 2-2′-(*p*-phenylene)-bis-benzothiazole resulted m. p., 263° cor. which was practically odorless.

Hofmann[6] first prepared bis-benzothiazole (oxalamidothiophenol) by fusing acetanilide with sulfur. It was one of the many products of the reaction, and the yield was very poor. It may also be prepared by passing cyanogen[14] into an alcohol solution of *o*-aminothiophenol. Very good yields have resulted from a fusion of the zinc salt of *o*-aminothiophenol and oxalyl chloride,[27] giving colorless plates from boiling toluene.

Di-*o*-aminophenyl-disulfide on treatment with pyromucyl chloride gave greenish yellow crystals of bis-(pyromucylanilide) -*o*-disulfide. In a similar manner di-*o*-aminophenyl-disulfide and α-thienyl chloride gave fine yellow prisms of bis-(α-thiophenanilide)-*o*-disulfide. Both these compounds on reduction with tin and hydrochloric acid gave respectively 2-α-furyl-benzothiazole and 2-α-thienyl-benzothiazole.

Condensation of di-o-aminophenyl-disulfide with acid anhydrides.

Di-*o*-aminophenyl-disulfide was condensed with 2 moles of phthalic anhydride at 130–150°. A reaction took place and water separated, condensing on the sides of the tube. The product, diphthalimido-phenyl-*o*-disulfide was a white, micro crystalline substance insoluble in aqueous sodium hydroxide.

Di-*o*-aminophenyl-disulfide was then condensed with succinic anhydride. The mass solidified during the heating, but there was no evidence of the splitting out of water. The product, bis-(succinanilic acid)-*o*-disulfide gave white, micro needles from alcohol, soluble in aqueous sodium hydroxide, indicating the presence of a free carboxyl group.

The reaction between glutaric anhydride and di-*o*-aminophenyl-disulfide was similar. It gave a very similar product, soluble in aqueous alkali, bis-(glutaranilic acid)-*o*-disulfide.

The reaction between maleic anhydride and di-*o*-aminophenyl-disulfide took place at room temperature during the

grinding of the two substances together. The double bonds in the anhydride were evidently responsible for the increased activity. The product bis-(maleanilic acid)-*o*-disulfide was a yellow, micro crystalline solid, insoluble in the ordinary organic solvents. It was easily soluble in aqueous alkali, indicating the presence of a free carboxyl group.

On account of the therapeutic properties of camphor, it seemed worth while to prepare a compound from di-*o*-aminophenyl-disulfide and camphoric anhydride. On heating together the two substances, after a time the melt assumed a semi-solid state. The product, bis-(camphoranilic acid)-*o*-disulfide, gave greenish yellow crystals from alcohol. It was soluble in aqueous alkali again indicating the free carboxyl group. This anhydride reacted similarly to succinic, glutaric, and maleic anhydrides. The two carboxyl groups in camphoric acid differ in that one is joined to a carbon carrying a methyl group, while the other is not. It was not determined which carboxyl group was free and which was joined to the amino group, but each amino group carried a camphoric acid molecule.

It will be seen that phthalic anhydride reacted differently with the amino groups than the other anhydrides investigated and gave a different type of product.

Richard Meyer and Seeliger[19] studied the reaction of ethyl oxalate on aromatic amino compounds showing that an amide linking resulted with the elimination of alcohol.

On refluxing di-*o*-aminophenyl-disulfide with ethyl oxalate, we found that alcohol was liberated. Bis-(ethyl-oxanilate)-*o*-disulfide resulted. This compound on treatment with strong ammonia, immediately formed bis-(oxanilamide)-*o*-disulfide, fine white needles.

Bis-(ethyl-oxanilate)-*o*-disulfide on heating with aniline formed bis-(oxanilide)-*o*-disulfide also a white needle-like compound, showing that the reaction is a general one, applying to aromatic amines as well as to ammonia. Attempts to prepare a compound from ethyl oxalate and di-*o*-aminophenyl-disulfide in a I : I molar ratio proved unsuccessful.

Bis-(ethyl-oxanilate)-*o*-disulfide when treated with sodium in an alcohol solution gave a white precipitate, probably the sodium salt. This precipitate on treatment with dilute acid gave a fine needle-like precipitate of benzothiazole-2-carboxylic acid prepared formerly by Hofmann[16] and Reissert[24] by different methods. It decomposed on melting giving benzothiazole.

Experimental

Di-o-nitrophenyl-disulfide.

This was prepared according to Wohlfahrt[21] by treating an alcohol solution of *o*-chlornitro-benzene with an alcohol solution of sodium disulfide. Yields were less than those reported of 75%. The c. p. *o*-chlornitro-benzene (Eastman) gave a 60% yield of di-*o*-nitrophenyl-disulfide m. p., 195° cor. as reported by Wohlfahrt. The commercial *o*-chlornitro-benzene (Monsanto Chem. Works) gave a 56% yield m. p., 195° cor.

Zinc salt of o-aminothiophenol.

This was prepared according to M. T. Bogert and F. D. Snell.[42] A warm glacial acetic acid solution of the di-*o*-nitrophenyl-disulfide was treated with zinc dust until colorless, when the zinc salt was precipitated by dilution with two volumes of water. Yields were 90% as reported.

Hydrochloride of o-aminothiophenol.

This was first prepared by Hofmann.[8] It was prepared by the method of Claasz[29] as follows. Thirty grams of di-*o*-nitrophenyl-disulfide with 200 grams of 50% acetic acid and 200 grams of conc. hydrochloric acid and 85 grams of tin, were warmed on a sand bath under a reflux until a reaction started. On solution of the disulfide, the warming was continued until the tin was dissolved and the solution became clear. It was slowly diluted with hot water to about six liters, when the tin was precipitated with hydrogen sulfide and filtered off. On evaporation to a small volume the hydrochloride separated out. It was filtered off and washed with ether. It melted at 217° cor. with decomposition as reported.

Di-o-aminophenyl-disulfide.

It was prepared according to M. T. Bogert and F. D. Snell[44]

by passing a current of air through a suspension of the zinc salt of *o*-aminothiophenol in an ammonium hydroxide solution. Lustrous, light yellow plates m. p., 93° as reported. The yield was 57% a little less than the reported yield of 65%.

Reaction Between Aldehydes and *o*-aminothiophenol

2-Phenyl-benzothiazole.

One gram of the zinc salt of *o*-aminothiophenol was dissolved in 50 cc. of warm glacial acetic acid. One gram of benzaldehyde was added and a rapid stream of hydrogen sulfide gas was passed through the hot solution until the zinc was precipitated as zinc sulfide. When the precipitate settled, it was filtered off, and the clear, yellow solution on the addition of four to five times its volume of water gave a curdy yellow precipitate. This was filtered off and recrystallized from 50% alcohol with bone blacking to a constant m. p. It gave fine, lustrous, white needles m. p. 114° cor. with a pleasant, geranium like odor. Yield 0.8 gram (61.5%). The loss in crystallization was large. The melting point of 2-phenyl-benzothiazole reported by A. W. Hofman[2] was 115°. Jacobson[13] and Reissert[25] reported the melting point as 114°.

On account of the possibility of the 2-phenyl-benzothiazole being the oxidation product of 2-phenyl-benzothiazoline, an unsuccessful attempt was made to acetylate the thiazoline, if formed, thus preventing its ready oxidation. The warm glacial acetic acid solution of the benzaldehyde and the *o*-aminothiophenol after the separation of the zinc sulfide by filtration, was cooled and treated with excess acetic anhydride. There was no evidence of a reaction and the product on precipitation by the addition of water, gave on recrystallization from 50% alcohol, the 2-phenyl-benzothiazole m. p. 114° cor. as in the former case. Also the attempt to acetylate the precipitate immediately after its precipitation from the glacial acetic acid solution was unsuccessful, no reaction taking place and 2-phenyl-benzothiazole m. p. 114° cor. again resulted.

Analysis	C = 73.70%	H = 4.06%
Calc. for $C_{13}H_9SN$	C = 73.93%	H = 4.26%

2-(m-p-Methylene-dioxy-phenyl)-benzothiazole.

One gram of the zinc salt of *o*-aminothiophenol was dissolved in 50 cc. of warm glacial acetic acid and one gram of piperonal (heliotropine) was added. The procedure was identical with that used above in the case of benzaldehyde. The precipitate on recrystallization to a constant m. p. from 95% alcohol with bone blacking gave white, crystalline leaflets with a faint sweet odor m. p. 125° cor. Yield 1 gram (62.5%).

Analysis	C = 65.46%	H = 3.60%
Calc. for $C_{14}H_9O_2SN$	C = 65.85%	H = 3.53%

2-(p-Hydroxy m-methoxy phenyl)-benzothiazole.

Two grams of the zinc salt of *o*-aminothiophenol were dissolved in 100 cc. of warm glacial acetic acid and 2 grams of vanillin were added (1 mole of the zinc salt to 2 moles of the aldehyde). The procedure used above in the case of benzaldehyde was also followed here. The precipitate on recrystallization and bone blacking from 95% alcohol gave lustrous prisms with a slight vanillin type of odor and a constant m. p. 175.5° cor. Yield 1.5 grams (46.5%). It showed a purple fluorescence when dissolved in alcoholic alkali.

Analysis	C = 65.40%	H = 4.24%
Calc. for $C_{14}H_{11}O_2SN$	C = 65.32%	H = 4.28%

2-α-Furyl-benzothiazole.

Two grams of the zinc salt of *o*-aminothiophenol were dissolved in 100 cc. of warm glacial acetic acid and the zinc was precipitated by a rapid stream of hydrogen sulfide. The zinc sulfide was filtered off and to the cool solution, 1.22 grams of fural were added (1 mole of the zinc salt to 2 moles of the aldehyde). The solution was corked and let stand over night, then diluted with four to five times its volume of water. The precipitate was filtered off, bone blacked, and recrystallized from 60% alcohol and gave lustrous leaflets with a geranium or "rosenkörper" type of odor particularly noticeable when dissolved in alcohol. It gave a constant m. p. 105° cor. Yield of pure product 0.9 gram (36%).

The addition of the fural to the cool solution was not essential, but gave as good a yield and a product freer from impurity.

Analysis	C = 66.17%	H = 3.70%
Calc. for $C_{11}H_7ONS$	C = 65.67%	H = 3.50%

Benzothiazole.

Claasz[30] claimed the formation of benzothiazoline from formaldehyde and *o*-aminothiophenol hydrochloride. The exact procedure of Claasz was repeated as follows. Four and eight-tenths grams of the hydrochloride of *o*-amino-thiophenol were dissolved in 100 cc. of water. The solution was covered with 50 cc. of ether and 2.3 cc. of 40% formaldehyde solution were added. A curdy, yellow appearance resulted in the water layer. It was shaken with ether in a separatory funnel, the ether taking the yellow color. It was dried over calcium chloride and the ether removed by distillation. The residue was a thick, yellow oil. It was distilled in a vacuum and then redistilled under atmospheric pressure, the oil coming over entirely at 230–235°. A boiling point was taken by the method of Siwoloboff[12] giving 230–231°. This agreed with the boiling point of benzothiazole, prepared by Hofmann.[4] It had the characteristic odor of nitrogen bases and was soluble in carbon disulfide and alcohol, as was benzothiazole. Claasz reported benzothiazoline boiling point 270°.

2-Phenyl-benzothiazole.

The following procedure of Claasz[32] was repeated with benzaldehyde. One and six-tenths grams of the hydrochloride of *o*-aminothiophenol were dissolved in 20 grams of water. The solution was treated with 1.06 grams of benzaldehyde dissolved in 12 grams of dilute alcohol (50%). It was shaken and heated on the water bath for a half hour. A yellow oil separated and on cooling it partly hardened. It was recrystallized from 50% and 95% alcohol with bone blacking to a constant melting point and gave a white, needle-like product with the characteristic "rosenkörper" odor and a sharp m. p. 114° cor. It also gave a mixed melting point with some 2-phenyl-benzothiazole prepared by a different method[40] (from benzalaniline and sulfur) 114° cor. There was considerable loss in the recrystallizations necessary to produce a product with a constant m. p. Claasz reported a crystalline product, softening at 105° m. p.

108–109° as 2-phenyl-benzothiazoline. The product we obtained was undoubtedly 2-phenyl-benzothiazole, m. p. 114° cor.

2-(p-Hydroxy-m-methoxy-phenyl)-benzothiazole.

Following the procedure of Claasz,[33] 1.6 grams of *o*-amino-thiophenol hydrochloride were dissolved in 20 grams of water and a solution of 1.53 grams of vanillin in 33 grams of water was added, the mixture being heated on the water bath for a half hour. On cooling, the yellow oil solidified and it was filtered off and recrystallized from 95% alcohol with bone blacking to a constant m. p. 175.5° cor. Claasz reported a benzothiazoline, yellow flakes m. p. 163–165°. Our product gave a mixed melting point of 175.5° cor. with the 2-(*p*-hydroxy-*m*-methoxy-phenyl)-benzothiazole previously prepared, showing that the product was the benzothiazole. This product was identical in every respect with the product formerly prepared.

2-Phenyl-benzothiazole from benzal chloride.

An attempt to prepare the 2-phenyl-benzothiazoline from *o*-amino-thiophenol and benzal chloride resulted in the formation of 2-phenyl-benzothiazole. Two grams of the zinc salt of *o*-aminothiophenol were dissolved in 100 cc. of warm glacial acetic acid and 2 grams of benzal chloride were added. The solution was refluxed for a short time and as there was no evidence of a reaction, a rapid stream of hydrogen sulfide was passed through the solution to precipitate the zinc as sulfide. There was evidence of the evolution of hydrogen chloride. The zinc sulfide was filtered off and the clear, brown solution on treatment with four to five times its volume of water gave a precipitate. On recrystallization from 50% alcohol it gave fine, white needles with the typical "rosenkörper" odor and a constant m. p. 114° cor. A mixed melting point with some 2-phenyl-benzothiazole prepared by a different method[40] was also 114° cor.

Two grams of the zinc salt of *o*-aminothiophenol were heated with 2.04 grams of benzal chloride (1 mole of the zinc salt to 2 moles of the chloride) to boiling for a half hour. The fusion was treated with excess N sodium hydroxide and filtered. A large amount of tarry matter resulted which was practicaly

insoluble in 50% alcohol. On treatment with 50% alcohol a small amount of 2-phenyl-benzothiazole was obtained m. p. 114° cor. When mixed with 2-phenyl-benzothiazole prepared by another method[40] it melted at 114° cor.

Attempt to condense benzophenone chloride and o-aminothiophenol.

Since a benzothiazole had resulted from benzal chloride and *o*-aminothiophenol, an unsuccesful attempt was made to prepare a benzothiazoline from benzophenone chloride and the zinc salt. One and five-tenths grams of the zinc salt of *o*-aminothiophenol were dissolved in 100 cc. of warm glacial acetic acid and 2.1 grams of benzophenone chloride were added. A rapid stream of hydrogen sulfide was passed through the warm solution and the zinc sulfide was filtered off. On the addition of water to the acetic acid solution, benzophenone separated with a slight purple color. No condensation product could be recovered.

One and five-tenths grams of the zinc salt of *o*-aminothiophenol were heated with 2.1 grams of benzophenone chloride at 100° for two hours. A purple color developed changing to a light brown. On treating the mixture with water the zinc salt was precipitated unchanged.

One gram of the zinc salt of *o*-aminothiophenol was heated with excess benzophenone chloride (5 grams) at 150–170° in vacuo for one hour. A dark wine colored oil resulted. The oily material was washed with water and the excess benzophenone chloride was distilled off in vacuo, leaving a dark brown tar.

One gram of the zinc salt of *o*-aminothiophenol was heated with 1.51 grams of benzophenone chloride (1:2 molar ratio) for one hour in vacuo at 130–140°. A bright orange color developed. The oily material was washed with water and on treatment with alcohol considerable unchanged zinc salt precipitated. This was filtered off and on further evaporation of the alcohol more of the zinc salt separated. A small amount of oil remained, probably benzophenone chloride.

Attempt to condense ketones with o-aminothiophenol.

An unsuccessful attempt was made to prepare a condensation

product between Michler's ketone and *o*-aminothiophenol. One gram of the zinc salt of *o*-aminothiophenol was dissolved in 50 cc. of warm glacial acetic acid and 1 gram of Michler's ketone was added. A rapid stream of hydrogen sulfide was passed through the warm solution and the zinc sulfide was filtered off. A clear, dark, red solution resulted which on treatment with water gave a precipitate of Michler's ketone verified by a mixed melting point. There was no evidence of any condensation.

One gram of the zinc salt of *o*-aminothiophenol was dissolved in 50 cc. of glacial acetic acid and the zinc was precipitated with hydrogen sulfide, and filtered off. Two grams of acetone were added to the cool solution. The solution on treatment with water gave a small oily residue on neutralization. Cooling gave a white crystalline precipitate soluble in acid or alkali, but insoluble in alkali carbonate and the m. p. was only a little above room temperature. The substance was evidently *o*-aminothiophenol m. p. 26°. The oily residue was mainly uncrystallized *o*-aminothiophenol. The *o*-aminothiophenol rapidly changed to the di-*o*-aminophenyl-disulfide.

2-2'(p-Phenylene)-bis-benzothiazole.

Three grams of the zinc salt of *o*-aminothiophenol were heated with 1.94 grams of terephthalyl chloride[45] (1:1 molar ratio) with a small flame until a vigorous reaction began. Then the heating was continued in a boiling water bath for 1 to 2 hours. The product was powdered and treated with excess N sodium hydroxide and filtered. The residue was treated with several small portions of alcohol (5–10 cc.) in which the product was only very slightly soluble. The product was recrystallized with bone blacking from benzene to a constant m. p. 263° cor. It formed fine, colorless leaflets. Yield of pure product 2 grams (62%). The loss was largely in recrystallization.

Analysis	C = 70.77%	H = 3.78%	S = 18.33%
Calc. for $C_{20}H_{12}S_2N_2$	C = 69.76%	H = 3.49%	S = 18.63%

Bis-benzothiazole.

Hofmann[7] in 1880 first prepared this compound from acetan-

ilide and sulfur, but the yields were very poor. It may also be prepared from cyanogen[16] and *o*-aminothiophenol.

Three grams of the zinc salt of *o*-aminothiophenol were treated with 1.21 grams of oxalyl chloride[27] and the mixture was heated under a reflux condenser at 60–80° until a reaction started. After the reaction ended, the heating was continued on a boiling water bath for one hour. The product was finely ground and treated with excess N sodium hydroxide, and filtered. It was then treated with several portions of alcohol in which the product was very slightly soluble. The bis-benzothiazole was separated from the impurities by sublimation, forming very fine, white needles, very slightly soluble in alcohol. It was recrystallized from toluene and gave colorless, glistening plates. It dissolved in conc. sulfuric acid with the characteristic greenish yellow color. It gave a constant m. p. 300.5° uncor. Hofmann reported the m. p. as 300° while Lang[18] reported 304°. Yield of pure product 1.5 grams (60%).

Pyromucyl chloride from pyromucic acid.

L. Bodard[1] gave a method for the preparation of pyromucyl chloride from pyromucic acid and phosphorus pentachloride. Frankland and Aston[20] obtained good yields of the chloride by the use of a special apparatus. The following method of E. Baum[23] was used for the preparation of the pyromucyl chloride as there was less decomposition and better yields resulted.

Twenty-five grams of pyromucic acid m. p. 130° cor. (m. p. of the pure acid 132.6–134.3°) were heated with 65 grams of thionyl chloride (5 times the theoretical amount) on the water bath with a reflux for 2 hours. The excess thionyl chloride was distilled off and the distillation continued, the fraction between 170–175° being collected and redistilled. The pyromucyl chloride came over at a constant temperature 173–174°. Yield of pure product 23 grams (79%).

α-Thiophenic acid (*α-thiophene carboxylic acid*).

This acid was prepared according to M. G. L. Voerman,[26] as follows. α-Acetothienone (Kahlbaum) was oxidized by alka-

line potassium permanganate to α-thienyl glyoxylic acid. It was then oxidized to α-thiophenic acid with 30% hydrogen peroxide by the method of M. Holleman.[22]

$$C_4H_3SCOCOOH + H_2O_2 = C_4H_3SCOOH + H_2O + CO_2$$

The acid precipitated on acidification in an almost pure condition. It may be further purified by a vacuum distillation or by crystallization from water. Yield 9.7 grams from 11.8 grams of α-acetothienone (84%). The yield reported was about 80%. The m. p. of the acid obtained was 124–125°. The m. p. of the pure acid is 126.2°.

α-Thienyl chloride.

It may be prepared by the action of phosphorus pentachloride[17] on α-thiophenic acid,[11] similar to the production of benzoyl chloride. It was prepared according to Jones and Hurd.[39] Nineteen grams of α-thiophenic acid were treated with 50 grams of thionyl chloride. After refluxing, the excess thionyl chloride was distilled off and the α-thienyl chloride was obtained by fractional distillation. The chloride distilled over at 206–208° (boiling point of the chloride 206°). The yield agreed with that reported 19 grams (90%).

2-α-Furyl-benzothiazole.

Three grams of the zinc salt of *o*-aminothiophenol were heated to boiling with 2.5 grams of pyromucyl chloride (1 mole of the zinc salt to 2 moles of the chloride) for a half hour. The fusion was extracted with excess of N sodium hydroxide, filtered, and recrystallized with bone blacking from 50% alcohol to a constant m. p. It formed lustrous leaflets with a geranium odor, m. p. 105° cor. It gave a mixed m. p. 105° cor. with the 2-α-furyl-benzothiazole formed in a previous experiment from fural and *o*-aminothiophenol. The two products were identical in every respect. Yield of pure product 2.85 grams (75%). The loss was largely in recrystallization.

Attempt to convert 2-α-furyl-benzothiazole into the thiophene derivative.

One gram of 2-α-furyl-benzothiazole was finely ground with excess (about 5 grams) phosphorus pentasulfide and heated at

140–150° for three hours. It was then treated with excess 6N sodium hydroxide and warmed slightly. On filtering and recrystallization from 50% alcohol the 2-α-furyl-benzothiazole was recovered and gave a mixed m. p. with the initial material 105° cor.

The above procedure was repeated using a higher temperature, namely 195–205°, but in this case also the original 2-α-furyl-benzothiazole was recovered unchanged.

2-α-Thienyl-benzothiazole.

Three grams of the zinc salt of *o*-aminothiophenol were heated to boiling for a half hour with 2.8 grams of α-thienyl chloride (1 mole of the zinc salt to 2 moles of the chloride). The melt was extracted with N sodium hydroxide and filtered. The residue was recrystallized from 95% alcohol with bone blacking to a constant m. p. It gave needle like crystals, easily soluble in alcohol with a fairly strong geranium or "rosenkörper" type of odor. On slow crystallization well formed prisms resulted. The m. p. was 99.5° cor. Yield 2.3 grams of the pure product (56%).

Analysis	C = 60.93%	H = 3.56%
Calc. for $C_{11}H_7S_2N$	C = 60.82%	H = 3.22%

Bis-(pyromucyl-anilide)-o-disulfide.

Two grams of di-*o*-aminophenyl-disulfide were treated with 2.1 grams of pyromucyl chloride (1 mole of the disulfide to 2 moles of the chloride). A reaction immediately started. The mixture was heated in a boiling water bath for one hour. The fusion was extracted with excess N sodium hydroxide, filtered and recrystallized from 95% alcohol with bone blacking to a constant m. p. 160.5° cor. Yellow prisms resulted, easily soluble in warm alcohol. Yield of the pure product 2.3 grams (66%). The loss was largely in recrystallization.

Analysis	C = 61.18%	H = 3.50%
Calc. for $C_{22}H_{16}S_2N_2O_4$	C = 60.55%	H = 3.67%

Bis-(α-thiophenanilide)-o-disulfide.

Two grams of di-*o*-aminophenyl-disulfide were heated in a boiling water bath for an hour with 2.35 grams of α-thienyl

chloride. A reaction took place immediately on mixing. The fusion was extracted with excess N sodium hydroxide, filtered, and recrystallized from 95% alcohol with bone blacking to a constant m. p. 154° cor. Pale yellow, fine needles resulted. Yield of the pure product 2.5 grams (67%). The loss was largely in recrystallization.

Analysis	C = 56.50%	H = 3.56%
Calc. for $C_{22}H_{16}O_2S_4N_2$	C = 56.41%	H = 3.41%

2-α-Furyl-benzothiazole from bis-(pyromucyl anilide)-o-disulfide.

Eight-tenths gram of bis-(pyromucyl-anilide)-*o*-disulfide was heated to boiling with 5 cc. concentrated hydrochloric acid, 45 cc. of water, and 5 grams of granulated tin for a half hour. At the end of the time solution had occurred. It was made strongly alkaline with 6N sodium hydroxide and kept warm for an hour on the steam bath. On cooling the precipitate was recrystallized from 50% alcohol with bone blacking to a constant m. p. The product was identical with 2-α-furyl-benzothiazole. It melted at 105° cor. and gave a mixed m. p. 105° cor. with 2-α-furyl-benzothiazole prepared from the zinc salt of *o*-aminothiophenol and pyromucyl chloride. Yield of the pure product 0.6 grams (82%).

2-α-Thienyl-benzothiazole from bis-(a-thiophenanilide)-o-disulfide.

Eight-tenths gram of bis-(α-thiophenanilide)-*o*-disulfide was heated to boiling with 5 cc. of conc. hydrochloric acid and 60 cc. of water, and 5 grams of granulated tin. After boiling for from fifteen to twenty-five minutes a clear solution resulted which was made strongly alkaline with 6N sodium hydroxide and kept warm for an hour. On cooling the precipitate was filtered off and recrystallized from 95% alcohol to a constant m. p. 99.5° cor. It gave a product identical with 2-α-thienyl-benzothiazole and when mixed with it melted at 99.5° cor. Yield 0.4 grams (56%).

Reaction Between Acid Anhydrides and Di-*o*-aminophenyl-disulfide

Diphthalimidophenyl-o-disulfide.

Two grams of di-*o*-aminophenyl-disulfide and 2.4 grams of

phthalic anhydride (1 mole of the disulfide to 2 moles of the anhydride) were mixed and ground in a mortar. The mixture was heated at 120–135° for one hour. After about fifteen minutes heating, water boiled off condensing on the sides of the tube. The mass then solidified or set. After the heating, the solid substance was powdered and treated with three different portions of boiling 95% alcohol to remove any unchanged initial material, as the resulting compound was only very slightly soluble in alcohol. The compound was recrystallized with bone blacking from boiling benzene, in which it was moderately soluble. It gave a constant m. p. 219° cor. It was insoluble in water and aqueous alkali, and soluble in glacial acetic acid. It dissolved in 10% alcoholic alkali after a short refluxing. Subsequent treatment with acid and water gave a precipitate, which formed rhombic crystals of phthalic acid from dilute alcohol, showing that the phthalimide had been hydrolized. Yield of pure product 3.5 grams (85%). Qualitative tests for nitrogen and sulfur were positive.

Analysis	C = 66.18%	H = 3.03%
Calc. for $C_{28}H_{16}O_4N_2S_2$	C = 66.14%	H = 3.15%

Bis-(glutaranilic acid)-o-disulfide.

Two grams of di-*o*-aminophenyl-disulfide were well mixed with 1.84 grams of glutaric anhydride (1 mole of the disulfide to 2 moles of the anhydride). The mixture was heated at 100° for two hours. The molten mass solidified after a short heating, but there was no evidence of the splitting out of water. The mixture was treated with a small amount of benzene to remove any unchanged disulfide. The product was recrystallized to a constant m. p. from 80% alcohol with bone blacking. It gave very fine micro needles m. p. 155–156° cor. with slight coloration. On heating five degrees higher than the melting point there was considerable darkening showing decomposition. The compound was soluble in aqueous alkali (sodium hydroxide or sodium carbonate). Qualitative tests for nitrogen and sulfur were positive. Yield 3.5 grams (91%).

Analysis	C = 54.97%	H = 4.81%	S = 13.21%
Calc. for $C_{22}H_{24}O_6N_2S_2$	C = 55.46%	H = 5.04%	S = 13.44%

Bis-(succinanilic acid)-o-disulfide.

One and six-tenths grams of succinic anhydride were well mixed with 2 grams of di-*o*-aminophenyl-disulfide (2 moles of the anhydride to 1 mole of the disulfide). The mixture was heated at 120–130° for one hour. The molten mass solidified during the heating but no water separated. The product was finely ground and treated with several portions of chloroform to remove any initial products since the product was very slightly soluble in chloroform. It was recrystallized from 60% alcohol. It formed white, micro needles which turned yellow and drew away from the sides of the melting tube at 155–158° and melted at 167–168° cor. From very dilute alcohol it came down as a jelly-like substance resembling aluminum hydroxide. It was easily soluble in aqueous alkali indicating the presence of a free carboxyl group. It retained water tenaciously. Yield of pure product 1 gram (28%). The loss was largely in recrystallization. Qualitative tests for nitrogen and sulfur were positive.

Analysis	C = 53.45%	H = 4.92%
Calc. for $C_{20}H_{20}O_6N_2S_2$	C = 53.54%	H = 4.46%

Bis-(maleanilic acid)-o-disulfide.

Two grams of di-*o*-aminophenyl-disulfide were well mixed and ground with 1.58 grams of maleic anhydride. During the mixing, a slight warming was noted and the materials were reacting. The mixture was heated for one hour at 100–120°, but the reaction had evidently taken place in the cold as during the heating there was no melting of the constituents, indicating that a compound had formed with a higher melting point. The product was a fine, yellow, micro crystalline substance, insoluble in all the ordinary organic solvents as benzene, xylene, anisol, carbon disulfide, carbon tetrachloride, chloroform, alcohol 95% and absolute, amyl acetate, ethyl acetate, acetone, butyl alcohol, petroleum ether, ethyl ether. It was also practically insoluble in glacial acetic acid. It was easily soluble in aqueous alkali and hot nitrobenzene. From boiling nitrobenzene it came out with a slightly darker color probably due to decomposition at that temperature. It was recrystallized

from nitrobenzene heated only to 160° and gave a product melting with decomposition at 200–201° cor. and about two degrees higher it lost water forming a brown resinous substance. Yield 3.5 grams (97%).

Analysis	C = 54.87%	H = 3.67%	S = 14.02%
Calc. for $C_{20}H_{16}O_6N_2S_2$	C = 54.03%	H = 3.63%	S = 14.45%

Bis-(camphoranilic acid)-o-disulfide.

Two grams of the di-*o*-aminophenyl-disulfide were well ground with 2.94 grams of camphoric anhydride (1 mole of the disulfide to 2 moles of the anhydride). The mixture was heated at 130–140° for two hours and during this time the molten mass had taken a semi-solid state. It was treated with several portions of warm benzene in which the product was very slightly soluble, to remove any remaining initial material. The product was recrystallized from 80% alcohol to a constant m. p. It formed fine, greenish yellow, rhombic crystals soluble in aqueous alkali and melting at 229° cor. with decomposition. The yield of the pure product was 2 grams (40%). Qualitative tests for nitrogen and sulfur were positive.

Analysis	C = 62.71%	H = 6.52%
Calc. for $C_{32}H_{40}O_6N_2S_2$	C = 62.72%	H = 6.53%

Bis-(ethyl oxanilate)-o-disulfide.

Three and five-tenths grams of di-*o*-aminophenyl-disulfide were treated with 30 grams of ethyl oxalate and refluxed over a small flame for five hours. During the refluxing, alcohol separated, condensing on the walls of the air condenser. On cooling, the solution was treated with 50% alcohol to dissolve the excess ethyl oxalate. The resulting precipitate was filtered off and recrystallized from 50% alcohol with bone blacking to a constant m. p. 104° cor. The product formed yellow, lustrous plates, insoluble in water, but easily soluble in alcohol or ethyl oxalate. Yield 3.7 grams (68%).

Analysis	C = 53.31%	H = 4.44%
Calc. for $C_{20}H_{20}O_6N_2S_2$	C = 53.53%	H = 4.45%

Attempt to prepare a compound between ethyl oxalate and di-o-aminophenyl-disulfide in a 1 : 1 molar ratio.

Two grams of di-*o*-aminophenyl-disulfide were heated with 1.17 gram of ethyl oxalate (1 : 1 molar ratio) at 150° for two hours. A green tarry mass resulted evidently due to decomposition and no definite compound could be recovered.

In the second case, 2 grams of the disulfide were refluxed with 1 gram of ethyl oxalate in 25 cc. of xylene b. p. 140° for five hours. The xylene was removed by distillation and the last portion by evaporation. By repeated crystallizations from 50% alcohol the di-*o*-aminophenyl-disulfide was recovered melting at 93° cor. and giving a mixed m. p. with the original substance 93° cor. showing that no condensation had taken place.

Two grams of the disulfide were similarly refluxed with 1.17 grams of ethyl oxalate in 15 cc. of anisol b. p. 152° for three hours. The anisol was partly removed by distillation and the remainder by evaporation. On recrystallization from 50% alcohol, the disulfide was recovered m. p. 93° cor. When mixed with the original disulfide it melted at 93° cor.

Bis-(oxanilamide)-o-disulfide.

Five-tenths gram of the bis-(ethyl oxanilate)-*o*-disulfide was dissolved in 15 cc. of 95% alcohol. Excess conc. ammonium hydroxide was added and the white amino derivative immediately separated. It was filtered off and recrystallized from a large volume of 95% alcohol, appearing as very fine needles. The compound melted with decomposition at 240° cor. Yield 0.4 gram (93%).

Analysis	C = 49.66%	H = 3.92%
Calc. for $C_{16}H_{14}O_4S_2N_4$	C = 49.21%	H = 3.61%

Bis-(oxanilide)-o-disulfide.

Five-tenths gram of the bis-(ethyl oxanilate)-*o*-disulfide was heated with 10 grams of aniline for 2 hours at 150°. On cooling it was treated with 50% alcohol when a precipitate settled out. It was filtered off and washed well with alcohol. Then it was recrystallized from benzene and gave very fine, white needles melting with slight decomposition at 229–230° cor. Yield of pure product 0.3 gram (49%).

Analysis	C = 62.20%	H = 4.12%
Calc. for $C_{28}H_{22}O_4S_2N_4$	C = 61.99%	H = 4.05%

Benzothiazole-2-carboxylic acid.

This compound was first prepared by Hofmann.[16] It was also prepared by Reissert[24] by treatment of an alkaline solution of thio-oxanilic acid with potassium ferricyanide. It was described as forming white needles which on melting at 108° lost CO_2 forming a yellow oil, benzothiazole. The acid dissolved in acetone and on the addition of water it was precipitated forming crystals m. p. 105°.

One gram of bis-(ethyl-oxanilate)-*o*-disulfide was dissolved in 50 cc. of alcohol and treated with small pieces of metallic sodium. A white precipitate separated which was filtered off and dissolved in water. When the solution was made acid with hydrochloric acid, a precipitate settled out. It melted at 107° cor. and lost CO_2 forming a yellow oil with the characteristic odor of benzothiazole. A boiling point was taken of the oil giving 230° which proved it to be benzothiazole. The benzothiazole-2-carboxylic acid decomposed slowly in boiling water. When dissolved in acetone and precipitated by the addition of water it gave crystals m. p. 105° as reported. Yield 0.5 gram (60%).

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